REVIEW ARTICLE

Chronic pruritus associated with dermatologic disease in infancy and childhood: Update from an interdisciplinary group of dermatologists and pediatricians

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Abstract

An effective treatment strategy for chronic pruritus in children with dermatologic disorders should consider the multidimensional aspects of pruritus, the unique challenges associated with treating pruritic skin disorders in the pediatric population, and evidence-based therapies with demonstrated antipruritic benefits and clinically relevant effects on patient/family quality of life (QoL). The Course of Advanced Learning for the Management of ITch (CALM-IT) Task Force is an interdisciplinary group of experts specializing in core aspects of pruritus treatment, integrating pediatrics, dermatology, psychotherapy, pruritus management, and sleep. CALM-IT recently convened to provide updated guidance on managing chronic pruritus associated with dermatologic diseases in pediatric patients, with a special focus on atopic dermatitis (AD) and chronic spontaneous urticaria (csU). This review highlights the updated concepts and best practices, which were built upon international PRACTALL consensus and modified for children and infants with AD and csU. CALM-IT supports the routine use of basic skin therapy and the escalation of topical medications, according to severity and focused on rapid itch control. Anti-inflammatory agents should be appropriate for infants and children (i.e., with an optimized therapeutic index) and have proven antipruritic properties, such as those demonstrated by methylprednisolone aceponate. New experimental findings do not support the use of non-sedating oral antihistamines as adjuvant antipruritic therapy for AD. In csU, oral H_1-antihistamine use is justified, consistent with the distinct pathophysiologic mechanisms of itch underlying AD and csU. All encompassing QoL assessments should consider the burden of both patient and caregiver and should address outstanding unmet clinical needs of pediatric patients. Future research areas include integrated QoL assessments and multidisciplinary treatment programs with pediatric-targeted pruritic therapies providing rapid itch control.

CALM-IT task force

The Course of Advanced Learning for the Management of ITch (CALM-IT) Task Force is an interdisciplinary group of experts specializing in core aspects of pruritus treatment: pediatrics, dermatology, psychotherapy, chronic pruritus management, and sleep. In February 2012, CALM-IT convened in Berlin, Germany, to develop an updated tool for practicing physicians managing chronic pruritus associated with dermatologic diseases in pediatric patients. The core objectives of the expert group meeting were the following: (i) discuss chronic pruritus as the predominant clinical feature of atopic dermatitis (AD) and chronic spontaneous urticaria (csU), (ii) realize the impact of itch on the quality of life (QoL) in both pediatric patients and their families, (iii) define the unmet needs in the clinical management of pruritus, and (iv) develop this joint publication on the treatment of chronic pruritus in children with skin disorders, such as AD and csU. Although chronic pruritus is associated with a number of both dermatologic and non-dermatologic disorders, this discussion focuses primarily on two dermatologic conditions, AD, and csU. Chronic pruritus is the predominant clinical feature of both diseases,

and the distinct pathophysiologic pruritic mechanisms underlying each of these diseases highlight the need for a modern and individualized approach to managing chronic pruritus in pediatric patients. This updated perspective considers the multidimensional aspect of pruritus in common childhood skin disorders, the unique challenge in treating infants and children, and the most recent findings related to pruritus pathophysiology and targeted treatment. The members of this task force share a common belief that interventions focusing on fast pruritus relief and maintenance of symptom-free skin can better preserve QoL for children and their families. This approach can also facilitate regular therapy management and adherence. In this review, we recount the discussions leading to the current set of CALM-IT recommendations.

Definition of chronic pruritus

Pruritus (itch) can be defined as a poorly localized, non-adapting, usually distressing and unpleasant sensation that causes an intense desire to scratch (1). It can occur in acute or chronic (over 6 wk in duration) forms (1). In its chronic form, it may profoundly impact the quality of a patient's life. It mainly occurs with dermatoses, but can rarely occur with systemic diseases, such as renal or liver failure or genetic disorders (2). In children, chronic pruritus is most often associated with severe scratching and is a hallmark symptom of AD (atopic eczema, eczema, neurodermatitis). The focus of this review is on the chronic form of pruritus, as it is the form that most severely impacts other dimensions of well-being for patients, such as QoL.

Classification of chronic pruritus

Several pruritus classifications that consider the different etiologies and clinical morphologies of chronic pruritus have been published. The International Forum for the Study of Itch (IFSI) has proposed a classification system for distinguishing three groups of patients with chronic pruritus based on clinical and differential diagnostic reasons (3). The first group (Group I – pruritus on primarily inflamed skin) includes patients with underlying dermatologic diseases; the second (Group II – pruritus on primarily non-inflamed skin) and third (Group III – pruritus with chronic secondary scratch lesions, such as prurigo nodularis) groups include patients with systemic diseases, for example diseases of the kidney and liver, pregnancy- and drug-induced pruritus, and neuropathic and psychiatric diseases.

Qualities and course of chronic pruritus

Patients with chronic pruritus report various qualities associated with pruritus. Selected dermatologic and systemic diseases commonly associated with pruritus, as well as a description of the associated pruritus symptoms, are described in Table 1 (4). These include pure itching, itching after mechanical stimuli, aquagenic pruritus, or mixed symptoms with itching, pain, burning, or stinging (4–6). Along with course and site of onset, there are characteristic sensory patterns for different forms of pruritus, which are referred to as 'clinical sensory characteristics'. Characterizing pruritus in terms of the localization (generalized or localized), the time course, determining when

Table 1 Qualities and characteristics of pruritus in selected dermatologic and systemic diseases commonly diagnosed in children (5)

Diagnosis	Patient history and affected site	Qualities and course of itch
Skin diseases		
Atopic dermatitis	Pruritus with flare-ups or in the interval in between	Daily itch between 30% and 90% with a peak occurrence at evening and during the night that carries a high emotional burden. Sharp, stinging, burning, and pruritus exacerbation after scratching, tickling, prickling; allokinesis (pruritus after non-pruritogenic stimuli)
Chronic spontaneous urticaria	Purely itching with edema, erythema	Histamine-mediated pruritus, sometimes mechanically induced, scratching is avoided
Psoriasis	Limited to the psoriasis plaques	Itching only
Systemic diseases		
Kidney disease requiring dialysis	2–3 months after beginning dialysis, generalized or localized (back, face, shunt area), often additional xerosis, often prurigo	Purely itching, occasionally attacks of itching or stinging during or just after dialysis, often very severe
Cholestatic diseases	Generalized pruritus, especially on distal extremities; typically triggered by tight clothing; few lesions from scratching	Purely itching; can be mechanically induced; not diminished by scratching, scratching is avoided
Polycythemia vera	Generalized pruritus, possible prurigo	Stinging, aquagenic itching: pruritus after contact with water, temperature change
Hodgkin's disease	Pruritus in inflow area of affected lymph nodes, generalized in conjunction with mediastinal sites, premonitory onset	Itching only

the pruritus started, whether the pruritus is continuous or intermittent, whether there has been an increase or a decrease in symptoms, or whether there are daily or seasonal changes in the presence and qualities of pruritus will help determine the most adequate management strategy.

Pathogenesis of acute and chronic pruritus

Pruritus is regularly reported in the general population (lifetime prevalence, 22%) (7) and is the most frequently described symptom in dermatology. There are different triggers for pruritus, such as stress, sweating, exercise, xerosis, and food that can activate or modulate the sensory nerve fibers involved in pruritus (4). Physical stimuli, such as heat and cold, modulate the perception of itching; painful heat and cold can significantly diminish it, while moderate cold intensifies it (8).

Pruritus involves various cellular networks, including T cells and eosinophils, keratinocytes, mast cells, and sensory nerves (4). The latter, specifically subsets of C fibers (peripheral) and spinal projections (central), are the main players in the transmission of pruritus, consistent with an observed lack of itch where there are no nerves. Pruritus can be mediated by various inflammatory and non-inflammatory stimuli, including histamine, proteases, gastrin-releasing peptide (GRP), mu opioids, substance P, and interleukin 31 (IL-31). Although the sensory neurons responsible for itch transmission are also nociceptive, recent evidence from neurons that express itch-specific receptors (i.e., gastrin-releasing peptide receptor) suggests the existence of pruritus-specific pathways in both the central nervous system and in fibers localized to the epidermis (Fig. 1) (9–12). Over time, large-scale activation in regions of the brain involved in central sensitization can be observed in chronic itch (13).

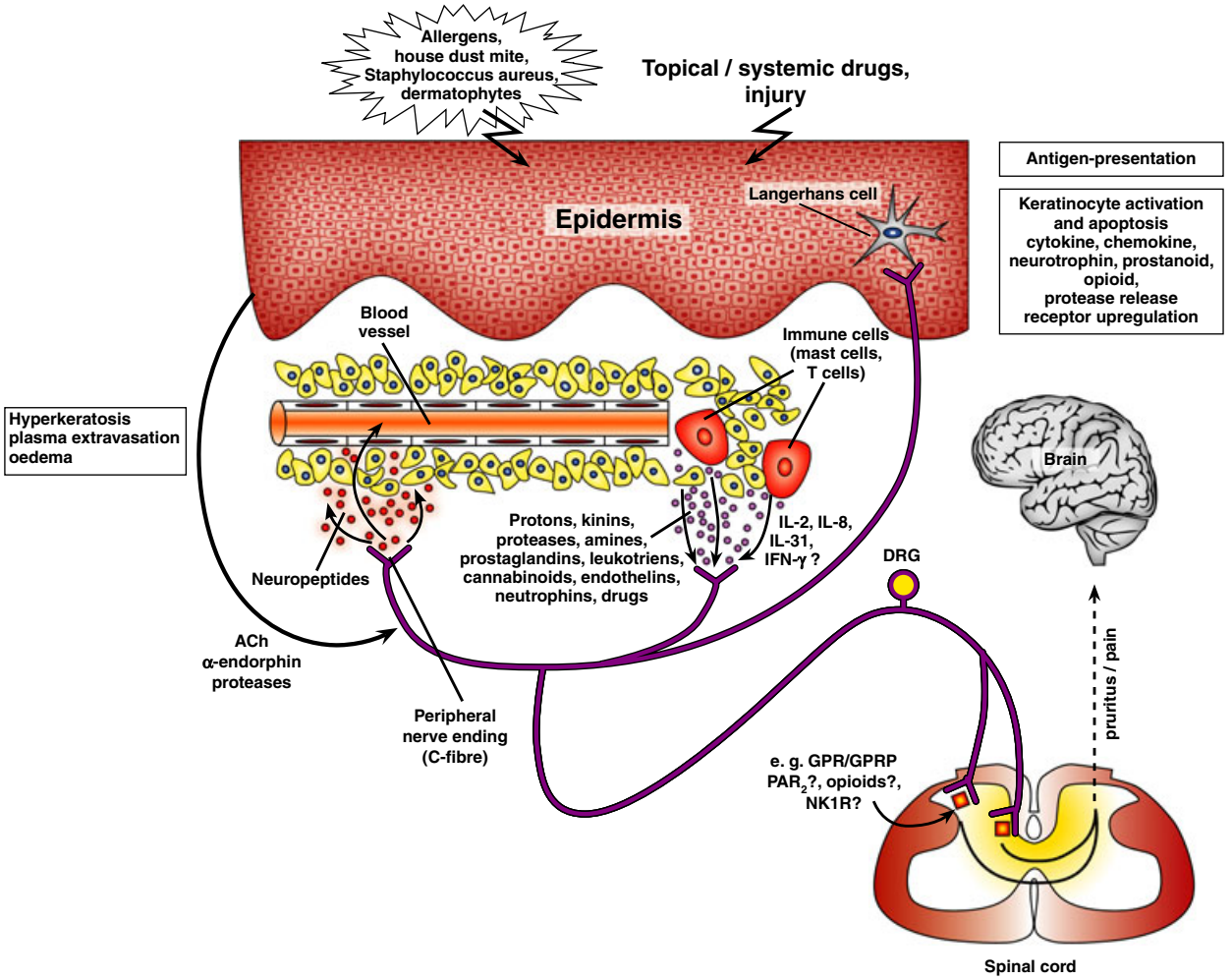

Figure 1 Neuroanatomic and neurophysiologic pathways of pruritus (10, 12, 138). Stimulation of itch-specific receptors occurs at the dermal–epidermal junction by inflammatory and non-inflammatory stimuli mediators that include histamine, kinins, interleukins, proteases, neuropeptides, prostaglandins, cysteine, proteases (such as mucunanin, cathepsin S), gastrin-releasing peptide (GRP), mu opioids, substance P, and interleukin 31. Sensory cutaneous nerves transmit the signal to dorsal root ganglions, reaching the spinal cord and the brain. Figure adapted from Buddenkotte and Steinhoff (10), and reproduced with the author's permission.

Diagnostic approach – clinical parameters of chronic pruritus

Diagnostic steps

The current guidelines for diagnosing and classifying skin disease-associated chronic pruritus in adults align closely to the guidelines created for the respective skin disorder and can be appropriately applied to children (1). When possible, it is important to determine the clinical parameters of pruritus, such as the localization, time course, onset, continuous or intermittent patterns, increased or decreased symptoms, daily or seasonal changes in the presence/quality of pruritus, and triggering factors. In chronic pruritus, other subjective questions should be asked about the patient's scratching behavior to assess the QoL impairment that results from pruritus. The qualities of pruritus can also facilitate a diagnosis. For example, the pruritus associated with AD is often characterized as a sharp, stinging, burning, tickling, and/or prickling itch that usually peaks in the evening or at night – a high emotional burden leading to a corresponding QoL impairment – and daily occurrence on 30–90% of the body surface.

Clinical attempts to differentiate systemic causes of skin disease-associated pruritus (e.g., AD, psoriasis, etc.) from local causes of pruritus (e.g., insect bites, contact dermatitis) should be made (Table 2). When etiology has been identified, appropriate guideline-based treatment should be applied (14).

Pruritus in atopic dermatitis

Atopic dermatitis is a chronic relapsing inflammatory and intensely pruritic skin disease of unknown origin occurring often in families with atopic diseases (i.e., AD, bronchial asthma, and/or allergic rhinoconjunctivitis). AD is one of the most common skin diseases and is characterized by pruritus, eczematous lesions, xerosis, lichenification, and a close association with IgE-mediated sensitization to aeroallergens and foods (15). The cumulative prevalence of AD in children varies greatly from region to region and has been reported to range from 8% to 20% (2, 16). As demonstrated by the International Study of Asthma and Allergies in Childhood (ISAAC), AD continues to increase worldwide (17, 18). AD is observed primarily during infancy, with 38% of all cases of AD beginning before the age of 3 months (2), 45% within the first 6 months after birth, 60% during the first year and 85–95% before 5 yr of age (2, 19).

Pruritus and xerosis are key elements of AD; without them, an AD diagnosis should be questioned. Outside of these symptoms, the diagnosis of AD is based on a personal and/or family history of atopy, coupled with the clinical signs and symptoms (20, 21). In infants and young children, the main symptom of AD is severe pruritus affecting mostly the face, hairy scalp, and lateral extremities. In older children, the typical clinical picture of AD develops with eczema in the flexural parts of the arms and legs (15).

After a diagnosis of AD is established, monitoring of the disease course and response to treatment should be performed based on patient-relevant outcome measures (22). An international consensus study involving patients, pediatricians, and dermatologists emphasized the importance of monitoring AD symptoms (i.e., pruritus) in routine care (23). The Scoring of Atopic Dermatitis (SCORAD) Scale is one validated instrument recommended for the assessment of clinical signs and symptoms (i.e., pruritus and sleeping problems) (24).

Pruritus in chronic spontaneous urticaria

CsU is a common and extremely distressing pruritic dermatologic disease causing severe impairment in many facets of everyday life (25, 26). CsU is defined as the daily or almost daily occurrence of recurrent, transitory, and highly pruritic wheals with or without accompanying angioedema over more than 6 wk (27). Urticaria can occur in all age groups; however, csU appears to be less common in children than adults, affecting 0.1–0.3% of children (28). In adults, urticaria may affect up to one in four individuals in their lifetime, while point prevalence for csU ranges from 0.5% to 1.0% (29). Although causal factors for csU are generally elusive and are most frequently attributed to the condition in adults, csU during childhood can often be attributed to autoreactivity. Food allergy and intolerance, as well as infections, have been shown to be additional potential underlying causes; however, evidence from well-controlled studies to support those respective associations in children is currently lacking (28). CsU is a source of pruritus in only approximately 3% of children (30), but it presents a major clinical unmet need with regard to our understanding of its causes/triggers, pathophysiology, characterization, and optimal treatment in this particular population.

The 2009 guidelines for urticaria recommend using the same diagnostic procedure for adults as for children (31–33), because of the similarities between the underlying putative cause of csU in both populations (34). A simple scoring system based on the characterization of key urticaria symptoms (wheals and pruritus), the urticaria activity score (UAS), is used to assess disease activity (35).

Chronic pruritus assessment

There is no standardized method of documenting chronic pruritus in children. Severity, duration, and intensity of pruritus can be measured using different scales appropriate for older (>6 yr of age) children, such as the visual analogue scale (VAS), numerical ratio scale (NRS), or verbal rating scale (36). As noted above, chronic pruritus is defined as lasting more than 6 wk (1).

Most methods of chronic pruritus assessment are problematic because they fail to consider the frequency of itch attacks over the course of a day and almost never assess the impact of pruritus on functional aspects of daily life (37, 38). Examples of more pruritus-appropriate assessments include the Itch Severity Scale (ISS) (39), Eppendorf Itch Questionnaire (40), 5-D Itch Scale (41), Patient-Oriented Eczema Measure (42), and SCORAD (e.g., insomnia, pruritus domains) (24).

Evaluations of pruritus should not only focus on the intensity of itch, but also on how the symptom is perceived by the patient. Therefore, a practical questionnaire assessing pruritus severity and resulting patient burden is required for both clinical evaluation and research (39). Recently, a consensus

Table 2 Examples of differential diagnoses of pruritus in children (2)

Dermatoses (in order of decreasing frequency)	Systemic diseases	Neurogenic and psychogenic diseases (rare in children)
Infectious diseases by bacteria, viruses or fungi	Renal disease	Skin-picking syndrome (e.g., prurigo nodularis)
Urticaria	Hepatic disease	Depression
Atopic dermatitis	Hematologic disease	Obsessive–compulsive disorders
Psoriasis vulgaris	Drug-induced exanthemas/pruritus	Schizophrenia and other psychoses (e.g., delusional parasitosis)
Epizoonoses, for example, scabies, insect bites, pediculosis	Neoplastic disease	Tumors or abscesses of the CNS
Mastocytosis	Endocrine disease	
Autoimmune disease (e.g., collagenoses, dermatitis herpetiformis, IgA linear dermatitis)	Histiocytoses	
Genodermatoses (e.g., neurofibromatosis)	HIV/AIDS	
	GvHD	

GvHD, graft-versus-host-disease.

Table 3 Suggested domains for inclusion in a multidimensional itch questionnaire (43)

Dimensions of pruritus	Questions
Localization	Where is the itch?
Frequency of itch	How often does the itch occur (e.g., daily, weekly)?
Duration of itch	How long has the itch been present (e.g., minutes, hours, days)?
Intensity	VAS, NRS, VRS, ISS, EASI, SCORAD
Sensory qualities	What does the itch feel like (e.g., pure itch, stinging, burning, mixed sensation)?
Scratch response	Rubbing, squeezing, pinching the skin
Opinion on origin	Patient's personal view
Affective dimensions	Bothersome, unbearable
Aggravating or relieving factors	What makes the itch better or worse?
Disability/impairment	How does the itch affect the patient and family's everyday life?
Response to current and previous treatments	How effective have drugs and other treatments been?
Coping	Itch-specific coping styles
Itch cognitions	Catastrophizing and problem-focused coping
Quality of life	Use VAS for screening or CDLQI

CDLQI, Child Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ISS, Itch Severity Scale; NRS, numerical ratio scale; SCORAD, SCORing of Atopic Dermatitis Scale; VAS, visual analogue scale; VRS, verbal rating scale.

paper from the IFSI put forward recommended domains to be included in itch questionnaires to better assess chronic itch and guide therapy (Table 3) (43). Researchers agree that standardizing the methods of evaluating pruritus with itch questionnaires that assess the multidimensional nature of the symptom is of prime importance (44).

Especially in the context of chronic pruritus, there is a need to consider the QoL of both the child and the family through health-related QoL assessments focused on skin disorders and/or the pediatric population and those that account for patient and family burden level. Persistent and high scores obtained with these questionnaires should sound an alarm and be aggressively addressed with focused pruritus management. Examples of recommended scales include Skindex-16 (45), Skindex-Teen (46), Childhood Atopic Dermatitis Impact Scale (47), Infant's Dermatology Life Quality Index (48), Children's Dermatology Life Quality Index (49), and ItchyQoL (50). Instruments that measure the effect of the families' QoL include the Dermatitis Family Impact Questionnaire (51). Other pruritus disease-specific questionnaires are available for disorders other than AD, such as the CU-Q_2oL for csU (52–55).

Impact of chronic pruritus on QoL, sleep, and adolescent development

Chronic pruritus has a profound impact on both the QoL of the patient and the family. Symptoms of AD, such as pruritus, have been identified as a recommended core outcome domain for AD trials and as the most important outcome domain for health services research by an international multiprofessional expert panel (23, 56). Recently AD has been identified as being related to attention deficit hyperactivity disorder in different epidemiologic studies (57–60). Children with AD and chronic pruritus have also been shown to be at increased risk for anxiety, depression, feelings of helplessness, frustration, and suicidal thoughts (61–64).

It is also important to appreciate the levels of disease-related distress placed upon the parents and caregivers of pediatric patients with chronic pruritus. For instance, parents of children

who have AD reported greater stress levels than parents of children with other chronic diseases, such as diabetes mellitus (65). Parents have reported both high stress related to treating and taking care of the child with AD and feelings of helplessness regarding the child's symptoms (51). The burden of AD in children can disrupt family and social relationships, in addition to interfering with a child's recreational activities and schooling. The burden of caring for the child with AD can also negatively affect spousal relationships and interfere with adequate attention to siblings (66).

The profound impact of csU on QoL is rarely addressed in clinical studies (28). A csU-specific QoL questionnaire is currently being used to evaluate the effects of csU in adults; however, to date, the questionnaire has not been adapted for children (28). A recent study conducted in Spain reported that csU could have a significant effect on children's education (67), as it is not uncommon for children to miss days of school because of the perception that the condition is infectious or allergic and the fear that the child is not well (28, 68). Furthermore, a small percentage of the parents of children with csU had to take time off from work to care for their child (67).

The consequent (sometimes unconscious) scratching response elicited by chronic pruritus (part of the 'itch–scratch' cycle) can disrupt sleep quality with frequent awakenings and reduced sleep efficiency, which result in increased tiredness throughout the day (69–72). Sleep disorders are an important negative effect of pruritus in AD and are especially relevant in children and adolescents (73), and even in infants with AD (74), and those who experience sleep problems are at increased risk of developing emotional and conduct problems in adolescence (59). Eventually, fragmented and prolonged sleep loss can have a deleterious effect on the physical and emotional well-being and social functioning of both the pediatric patient and their family (75, 76).

The multidimensional nature of chronic pruritus gains greater importance with the recent finding that the impact of chronic pruritus on QoL is on a par with chronic pain syndromes (77). Because of the major impact that chronic itch has on the QoL of patients and their families, dermatologists should better integrate QoL measures to inform and improve clinical decision making, and in the end, positively affect the patient's prognosis (78).

Management of chronic pruritus

Natural course of atopic dermatitis

The natural course of AD shows that incidence peaks in infancy and the prevalence is particularly high during the first 2 yr of life, and disease activity often subsequently declines. Thereafter, AD remains a major risk factor for the development of rhinitis and asthma (79). Approximately half of all patients with AD, particularly those with severe AD, subsequently develop asthma (80). The increased risk of asthma at ages 6–7 yr for children with AD has been quantified prospectively in several longitudinal studies comparing children with and without AD. There are ample data to suggest that a multifactorial sequence of atopic manifestations occurs: AD in infancy followed by allergic rhinitis and/or asthma in later stages (79–92). This characteristic change of phenotypes from infancy to adolescence has been described as the 'atopic march'.

Current therapeutic approaches for chronic pruritus in AD

Adequate therapy should address both the pathophysiologic and emotional component of AD-related itch to alleviate problems with disease management and adherence to therapy in children. Treatments for pruritus in children and infants with skin disorders should ideally focus on the cause; however, obtaining accurate descriptions of itch is intrinsically more difficult in children (93, 94). Basic therapy is focused on hydrating topical treatment and avoidance of specific and unspecific provocation factors (1, 94). If possible, there should be active identification and elimination of exacerbating factors, such as inhalants, microbial agents, autoallergens, foods, and emotional stress. The current recommended approach to treating chronic pruritus includes the stepwise, personalized management composed of general (basic therapy) measures, specific measures, and systemic treatment. Treatment selection must be made based on individual symptoms, and treatment switches (step-up and step-down) may be needed based on individual treatment responses and disease activity.

Specific treatments include emollients and anti-inflammatory topical therapies, such as topical corticosteroids (TCSs) and calcineurin inhibitors (TCIs) (1, 94). In AD, TCSs remain the mainstay of therapy, but TCIs, such as tacrolimus and pimecrolimus, may be preferred in certain sensitive skin locations in children over the age of 2 yr, despite residual long-term safety concerns. Systemic therapy includes anticonvulsants, opioid receptor antagonists or agonists, antidepressants, antiemetics, and immune-suppressive treatment (for severe cases) (1, 94).

Clinical and pathophysiologic rationale for oral antihistamine use

Systemic antihistamines, such as H_1-receptor antagonists, have been used for decades in an attempt to relieve pruritus in conditions like AD (95), despite the fact that the few randomized controlled trials conducted for this purpose have shown only a weak or no effect in reducing pruritus in AD (Table 4). Therefore, more recent AD guidelines have concluded that there is not enough evidence to support the general use of either first- or second-generation (H_1) antihistamines for treatment of pruritus (96, 97).

The relative ineffectiveness of oral antihistamines in treating pruritus associated with diseases like AD can be explained, in part, by recent pathophysiologic findings on the pathways responsible for histaminergic and non-histaminergic pruritus. That is, the pruritus associated with AD is pathophysiologically distinct from the pruritus associated with csU (98, 99). Emerging data from the experimental cowhage-induced itch model points to a histamine-independent pathway mediated by the proteinase-activated receptor (PAR-2) as the major component of pruritus associated with chronic AD (99). The itch fibers stimulated by cowhage are distinct from the histaminergic

Table 4 Clinical data on antipruritic therapy of atopic dermatitis (EDF guidelines) (1)

Antipruritic therapy in AD (130)	
Antipruritic effects confirmed in controlled studies	Glucocorticosteroids (topical and oral) Calcineurin inhibitors: cyclosporin A, tacrolimus ointment (2×/day), pimecrolimus cream (2×/day) (104) (135) Leukotriene antagonists (zafirlukast) Interferon gamma, immune complexes Doxepin 5% cream (2×/day) (131, 132)
Uncertain results	Antihistamines (topical and systemic) Naltrexone 50 mg/day (133) Mycophenolate mofetil (MMF) (134, 135)
Antipruritic effects confirmed in case reports	Macrolide antibiotics Immunoglobulin, intravenous UVA1-/UVB 311-therapy Capsaicin (3–5×/day)

AD, atopic dermatitis; EDF, European Dermatology Forum.

fibers associated with chronic urticaria pathways (98). Furthermore, a recent study imaging brain activation suggests that distinct neuronal networks are involved in the processing of these two different types of itch (100). Therefore, there is no mechanistic rationale for treating non-histaminergic pruritus–related AD with antihistamines (1).

Treatment guidelines do, however, support the use of antihistamines in a subgroup of affected children with the histaminergic pruritus associated with csU (94).

Optimizing topical treatment

Topical treatment-related challenges in children and infants include an increased surface-to-volume skin ratio, which leads to increased absorption of any active ingredient applied to the skin (101). In addition, children have slower drug metabolism than adults, which has led to a significantly higher level of serum cortisol after treatment with traditional hydrocortisone therapy compared with older patients (102). Newer formulations of TCSs, the gold standard in AD therapy (1), have resulted in the emergence of fourth-generation products with an optimized therapeutic index, a measure that describes the balance between potency and adverse events. Several fourth-generation TCSs have been studied in pediatric AD trials and have shown encouraging results of equal or greater efficacy than traditional TCSs and TCIs, but similar or fewer adverse events (103). Methylprednisolone aceponate (MPA), a fourth-generation, non-halogenated corticosteroid, has been extensively evaluated in children with mild, moderate, and severe AD in both the acute and maintenance settings. MPA has demonstrated rapid and efficacious symptom relief in AD in children and infants (within 2–3 days), with a low incidence of topical and systemic side effects (104).

Breaking the itch–scratch cycle

Rapid relief of itch should be a therapeutic priority for pediatric patients with chronic pruritus, given that improvement in QoL is an important unmet clinical need for these patients and their families. In typical studies of topical agents used in AD, onset of pruritus relief is characterized in units of days and weeks, a relatively long time frame for children (104). In addition, in studies supporting the current treatment recommendations for AD-associated pruritus, antipruritic effect was rarely the main research objective, but rather part of a total symptom score.

A recent pilot study suggested that MPA 0.1% was able to provide itch relief within hours in a nickel-induced pruritus model of allergic contact eczema (ACE) (105). In five of 10 volunteers, MPA treatment reduced pruritus VAS by 30% in the first 5 h following treatment. This finding and the relative impact of this antipruritic effect on QoL require confirmation in larger studies with patients with ACE and/or AD. However, the preliminary results of this study highlight that insights into the short-term antipruritic potential of topical agents are limited by study design and that the pursuit of immediate itch relief for children has not yet received the attention it deserves. There is a need to raise awareness of the benefit of rapid itch control for pediatric chronic pruritus, especially with the use of existing pharmacologic therapies suitable for this population. Research efforts should also include the development of more targeted therapies for pruritus that are safe for children and infants.

The pruritus in AD, for example, elicits a scratch response and initiates the 'itch–scratch' cycle, which in turn aggravates flares and pruritus, exacerbating the severity of the skin disease and causing further complications (106). As chronic scratching also represents a factor that triggers and perpetuates the itch–scratch cycle, the most important step in the management of the AD patient is the rapid interruption of itch by an effective symptomatic topical and/or systemic therapy.

Psychological intervention

The complications of itch extend beyond just the physical domain. In addition, there are unique challenges intrinsic to the pediatric treatment of pruritus: subjective nature of itch

assessment, impact on QoL, sleep, behavior and development, impact on the entire family, adherence to therapy, and the risk of atopic march in patients with AD.

It is well known that stress and excitement can affect the course of dermatoses by various mechanisms (i.e., neuromediators, increased IgE production). Psychological stress and symptoms appear to form a vicious cycle in AD (107) that can lead to psychological disturbances, such as stigmatization, social isolation, and discrimination (108). Furthermore, the pruritus-derived psychological distress in both adults and adolescents can lead to a prevalence of suicidal thoughts that increases significantly with increasing severity of itch (109, 110). Emotion and stress from chronic itch trigger a cycle of anger and frustration, leading to activation of neuropeptides. These molecules, in turn, provoke neurogenic inflammation in the skin and the degranulation and delivery of histamine, ultimately resulting in more itching and scratching, followed by more frustration and anger (111, 112). Therefore, it is not surprising that psychological interventions and programs have been reported to be more effective than some conventional treatments in terms of severity of eczema, subjective severity, and effect on QoL (113).

In addition to causal and symptomatic therapy, behavioral therapy to avoid scratching should be considered, for example, conscious suppression of the reflex by intense concentration, distraction, or alternative scratching techniques such as habit reversal (114). Adjuvant psychosocial programs are most effective in AD (114–117). Educational programs, which include strategies for breaking the cycle of itching and scratching, relaxation, and stress management techniques, as well as strategies for dealing with relapses, are useful complements for symptom management.

Educational approaches

Recent large-scale studies have highlighted the great clinical value in integrating multifaceted treatment approaches for pediatric patients with chronic pruritus and their families. Patient education that is effective in improving QoL and reducing the perceived severity of skin disease also reduces anger and frustration, allowing the patient to escape the cycle described earlier (118–120). Education programs for children with AD and their parents have demonstrated positive effects on disease severity and on the QoL of those affected by it (115, 121–127). There are several successful models of AD school programs worldwide (20), ranging from group lecture models (e.g., Asia) with broad reach but lacking individualized approach to highly individualized approaches (e.g., Canada) with less reach due to higher time demands. In Germany and France, group approaches that allow for a highly interactive learning experience have been implemented, but like many other programs, broad-reaching success has been limited by high logistic and organizational expectations. The patient education program tested in the German Atopic Dermatitis Intervention Study was found to have positive effects on disease severity, satisfaction with treatment and costs, coping behavior of children, parental management of the disease, and hospitalization rates (113, 115, 124, 128).

In the management of chronic pruritus in children, there is a need to improve access to existing and/or establish new multidisciplinary treatment programs that include at least the patient's pediatrician and the pediatric dermatologist, the nursing staff, and when possible, other specialties, such as pediatric psychologists or family therapists. For example, studies have shown an increased effectiveness with nurse-led workshops, highlighting the potential importance of a multidisciplinary team for the optimal management of patients with chronic pruritus (126, 129).

Summary of updated practical treatment recommendations from the CALM-IT task force

An integrated treatment strategy for the chronic pruritus associated with skin disorders must consider multidimensional aspects, the unique challenge associated with treating infants and children, and evidence-based choices of therapies with demonstrated antipruritic benefits and clinically relevant effects on patient/family QoL. Table 5 summarizes the recommendations culled by this international group of multidisciplinary experts (CALM-IT), which is built upon the international PRACTALL Consensus Report but modified for children and infants with AD and csU. CALM-IT supports the routine use of basic skin therapy to address dry skin and defects in the skin barrier. Subsequent pharmacologic management of symptoms should be on the basis of disease severity (mild-to-moderate, moderate-to-severe, recalcitrant/severe), and treatment of exacerbations should include the use of a mild followed by more potent topical medications, especially in the case of AD. When an anti-inflammatory agent is used, it should be one that is appropriate for infants and children and with proven antipruritic properties and an optimized therapeutic index, such as the fourth-generation MPA. Adjuvant antipruritic therapy for AD should not rely on the use of non-sedating oral antihistamines; however, if sedative and/or anxiolytic effects are clinically indicated or warranted, a sedating oral antihistamine could be considered. In csU, oral H_1-antihistamine use is justified; their demonstrated efficacy is consistent with a new understanding of the pathophysiologic mechanisms of itch underlying AD and csU. Patient-focused assessments of pruritus should be tailored to the input of either children or their caregivers. QoL assessments should be ongoing, considering the burden of both patient and caregiver, and used to address outstanding unmet clinical needs of pediatric patients.

Going forward, there are several management gaps that need to be addressed: (i) the need for more integrated QoL assessments that consider the QoL of both the child and the family, (ii) the need to improve access to/establish multidisciplinary treatment programs that include at least the patient's pediatrician and the pediatric dermatologist, the nursing staff, and possibly other specialties, such as pediatric psychologists or family therapists, (iii) the need to exploit the benefit of providing very rapid itch control, especially with existing pharmacologic therapies suitable for children, and (iv) the need to develop more targeted therapies for pruritic skin diseases that are safe for children and infants.

Table 5 Stepwise algorithm for effective management of infants and children with atopic dermatitis – and chronic spontaneous urticaria-related chronic pruritus: recommendations from the multidisciplinary CALM-IT task force. Table modified from the 2006 PRACTALL Consensus Report (136) and The EAACI/GA^{2}LEN/EDF/WAO Urticaria Guideline (137)

Selected pruritic skin diseases Intensity/Stage of AD*†	First-line therapy	Second-line therapy/Other	Other antipruritic treatments	Education and basic skin management
	Anti-inflammatory medications with antipruritic benefits			
Step 1 – Dry skin only	None	None	None	Educational programs (chronic nature of disease, importance of adherence to treatment, appropriate use/application of topical therapies), regular use of emollients, moderately heated water and synthetic detergents for cleansing, avoidance of triggers and allergens, diet (irritant-free/ elimination)
Step 2 – Mild-to-moderate AD	Low-mid potency TCS‡	TCI§	Antiseptics, oral sedating antihistamines,¶ phototherapy, psychosomatic counseling, climate therapy	
Step 3 – Moderate-to-severe AD	Mid-high potency TCS‡ with high TIX**	TCI§		
Step 4 – Recalcitrant, severe	Mid-high potency TCS‡ with high TIX**	Systemic therapy (e.g., cyclosporin A), hospitalization; azathioprine, oral tacrolimus (PUVA or UV therapy)††		
Chronic spontaneous urticaria	Oral non-sedating H_1-antihistamine (nsAH)¶	Weight-adjusted up-dosing (up to fourfold) of nsAH. If symptoms persist, add leukotriene antagonist or change nsAH In case of exacerbation, oral systemic steroid (for 3–7 days)	Add cyclosporin A, H_2-antihistamine, dapsone, omalizumab	

CyA, cyclosporin A; EAACI, European Academy of Allergology and Clinical Immunology; GA^{2}LEN, Global Allergy and Asthma European Network; PUVA, psoralen plus ultraviolet A treatment; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TIX, therapeutic index; WAO, World Allergy Organization; AD, atopic dermatitis.

*Health-related QoL assessments should focus on skin disorders and/or pediatric population and account for patient and family burden level.

†Clinical assessments of AD should include pruritus-focused scales and include, when possible, subjective domains, such as sleep disturbance and itch intensity.

‡When possible, use mild-to-moderately potent TCS for children and for application to sensitive areas of the face, genitals, or intertriginous areas. Always use with emollient therapy during acute flares.

§Use only in children >2 yr of age when TCS treatment has failed or is contraindicated. Do not use in immunosuppressed children.

¶Adjuvant antipruritic therapy in AD should rely on the use of antihistamines only if sedative and/or anxiolytic effects are indicated or clinically warranted. Oral non-sedating antihistamines are first-line treatment for chronic spontaneous urticaria.

**Fourth-generation TCS, such as methylprednisolone aceponate (MPA), is preferred.

††UV therapy, when indicated for children, should be performed with narrowband UVB (311 nm wavelength).

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